Open-label experience in Osteoarthritis and Rheumatoid Arthritis:

Study N49-96-02-024 is an ongoing, long-term open-label safety study of patients who previously participated in one of following nine phase II or III double-blind controlled studies:

- N49-96-02-012 (RA)
- N49-96-02-013 (OA)
- N49-96-02-020 (OA)
- N49-96-02-021 (OA)
- N49-96-02-022 (RA)
- N49-96-02-023 (RA)
- N49-96-02-054 (OA)
- N49-97-02-062 (OA/RA)
- N49-97-02-071 (OA/RA)

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All patients treated in the long-term open label study previously participated in one of nine controlled studies. A 14-day rule was used to determine direct transfer status as follows:

- If a patient received any celecoxib dose in the controlled study and transferred into the open label study within 14 days, the patient was considered a direct transfer patient and all previous study data were included in the long-term analysis (Day 1 of celecoxib is the first day of the double-blind study);
- If a celecoxib patient transferred after 14 days then Day 1 of celecoxib is the first day of the open label study
- Patients who received placebo or an active control agent in the double-blind study are evaluated as Day 1 of celecoxib in the open-label study regardless of the gap between studies.

This multicenter study is/was designed to determine the long-term (up to two years) safety, including an evaluation of the incidence of any clinically significant gastrointestinal events, of Cx administered to patients with osteoarthritis OA or RA. Efficacy assessments (see below) are also being performed. The data cutoff date for the interim data listings included in this NDA is November 21, 1997. The results of the completed trial are pending at this time; it is anticipated to be completed in 12/99.

For two-year patients, visits included the Baseline, at Weeks 2 and 6, and at Months 3, 6, 9, 12, 15, 18, 21, and 24. For patients enrolled for one year, the Month 12 visit is the final study visit. For both two-year and one-year patients, study visits are to include review of any treatment-emergent signs and symptoms experienced since the previous visit. Safety assessments are generally combined for OA and RA.

Measures of arthritis efficacy include:

- Patient's Assessment of Arthritis Pain on the Visual Analog Scale (VAS);
- Patient's Global Assessment of Arthritis;
- Physician's Global Assessment of Arthritis
- Functional Capacity Classification.

These assessments will be performed on all patients at every visit, with the exception of the Patient's Assessment of Arthritis Pain on the Visual Analogue Scale (VAS), with the exception of patients previously enrolled in N49-97-02-062 or N49-97-02-071. Patients will undergo a physical examination at the Baseline visit and every six months thereafter. Clinical laboratory tests will be performed at every study visit. Two-year patients will complete a quality of life assessment (SF-36 Health Survey) at Baseline and every six months thereafter, and a Health Resource Utilization Questionnaire at every visit except Baseline. One-year patients will not complete the SF-36 Health Survey or the Health Resource Utilization Questionnaire at any study visit.

A radiologic examination (i.e., hand and wrist x-rays for patients with RA and either the Index knee or the Index hip for patients with OA) will also be performed at Baseline and the Month 12, or Early Termination, visit for all patients, except those previously enrolled in N49-97-02-062 or N49-97-02-071.

As of the cutoff date, a total of 4499 patients had entered the long-term, open-label safety study. A total of 3256 patients were still active in the study at the cutoff date; the remaining 1243 had prematurely terminated from the study. The longest duration of treatment (patient 0150001) was 522 days.

The table below briefly summarizes the disposition of patients to this point for study 024:

Table 7: Disposition of Patients in Protocol 024

Category	Placebo	Cx (all doses)	NSAIDs	Total
Pts able to enroll	1270	4422	2073	7765
Pts enrolled (%)	860 (68)	2776 (63)	863 (42)	4499 (58)
Pts at 12 months	-	-	-	3256 (72)

Reviewer's comment: There is a discrepancy between the number of patients still active and those that have terminated between this text (i.e. 3256 and 1243, respectively) and tables cited below of 61 patients. In other words, the tables suggest there are 61 patients still receiving Cx that the text states have been terminated from study 024.

In study 024, the doses of Cx allowed have ranged from 100-200 mg BID for OA and 200-400 mg BID for RA. This range was allowed to control symptoms (increased) or for tolerability reasons (reduced). As can be seen (*Appendix*, *Table A.45*), approximately 70 % of patients with either OA or RA, increased their dose beyond what is felt to be the therapeutic dose during the randomized controlled studies presented in this NDA (i.e. 100 mg BID for OA, 200 mg BID for RA). Of those that did increase their dose, most moved to a dose twice as high (i.e. 200 mg BID for OA, 400 mg BID for RA).

Of the efficacy parameters assessed in protocol 024, the Patient's Global Assessment of Arthritic Condition for OA and RA are presented (see *Appendix*, *Figure A.1*); results are very similar for the Patient Assessment of Pain (VAS) and the Physician's Global Assessment for both the patients with OA and RA. Regarding figure 7 (OA) and figure 10 (RA) of Appendix figure A.1, it is noted by the sponsor:

"Although approximately 70% of OA patients did escalate the dose, there was no worsening of arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This data lends further support to the conclusion that celecoxib 100 mg BID is an efficacious dose and an increase to 200 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of OA."

"Although approximately 75% of RA patients did escalate their dose (to 300 or 400 mg BID), there was no evidence of worsening arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This finding lends further support to the conclusion that celecoxib 100 mg BID and 200 mg are efficacious doses and 400 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of RA".

Reviewer's comment: It could just as easily be argued that an escalation of the dose was required to maintain any long-term efficacy of Cx in OA and RA.

Appendix Tables/Figures

Table A.1 Schedule of Observations and Procedures (Protocol 020)

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±2 days	Week 12 Day 84 =2 days	Early Termination
Informed Consent	Х					- CITIM RELIGIO
Medical History	X				 	
Physical Examination	X				×	
Clinical Lab Tests (a)	X		X	X(b)	l 	X
QOL Assessment (c)		х	X		- x	X
OA Assessments	X(d)	X	×	<u> </u>	- Â	X
Discontinue NSAID or analgesic (e)	х			^_	<u> </u>	X
Meet Flare Criteria		X				
Signs and Symptoms	1	$\frac{\hat{x}}{x}$	×	×	- x	
APS Pain Measure (f)	 	X		- ^-	 	X
Patient Assessment of Function (I)		×				
Blood Samples for Plasma PK Levels (g)			х			
Dispense Study Medication		X	X	X		
Return & Count Study Med			Х	X	×	Х
Dispense Concurrent Medications Diary Card		×	Х	×		^_
Retrieve Concurrent Medications Diary Card			х	×	×	×

- Clinical laboratory tests included: Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]); and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). Serum pregnancy test for women of childbearing potential at Screening visit only.
- PT and PTT tests were not performed at the Week 6 Visit.
- SF-36 Health Survey.
- Screening Arthritis Assessment data were collected by Searle but not entered in the database.
- Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.
- American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. Patients enrolled in study prior to 8 August 1996 who already began taking study medication were not required to complete
- Three blood draws were to be taken from 200 patients (approximately 40 per treatment group) at selected sites between Day 7 and 28 after first dose for determination of SC-58635 plasma levels.

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Table A.2 Baseline demographics (study 020, 021, 054-pooled)

12-Week Pivotal Studies 020, 021, and 054)

			Celecoxib		Naproxen
	Placebo	50 mg BID	100 mg BID	200 mg BiD	500 mg BID
Baseline Characteristic	(n=664 ^a)	(n=671)	(n=644 °)	(n=648)	(n=631)
Baseline Demographic Ch	aracteristics				
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	(b)(4)				
<65 years - N (%)	361 (54%)	378 (56%)	358 (56%)	353 (54%)	334 (53%)
⊵65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin		1			
Asian ⋅ N (%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Caucasian - N (%)	577 (87%)	574 (86%)	569 (88%)	555 (86%)	553 (88%)
Hispanic - N (%)	22 (3%)	13 (2%)	7 (1%)	18 (3%)	11 (2%)
Other - N (%)	4 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Male - N (%)	198 (30%)	227 (34%)	203 (32%)	197 (30%)	201 (32%)
Baseline Index Joint and D	Disease Duration				
Baseline Index Joint					
Knee - N (%)	446 (67%)	455 (6 8%)	437 (68%)	435 (67%)	424 (67%)
Hip - N(%)	218 (33%)	216 (32%)	207 (32%)	213 (33%)	207 (33%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range (b)(4)				
<5 years - N (%)	257 (39%)	281 (42%)	255 (40%)	273 (42%)	264 (42%)
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

Table A.3 Baseline demographics (protocol 060, 087-pooled)

Week Pivotal Studies 060 and 087)

		Celecoxib			
Baseline Characteristic	Placebo (n=476) *	100 mg BID (n=474)	200 mg QD (n=454)		
Baseline Demographic Character	ristics		1 (1 10 1)		
Age (years)			T		
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62 0 (11 59)		
Range	(b)(4)		117 0 11 1 191		
<65 years - N (%)	260 (55%)	254 (540)	050		
≥65 years - N (%)	215 (45%)	254 (54%)	257 (57%)		
Race/Ethnic Origin	213 (4376)	220 (46%)	197 (43%)		
Caucasian - N (%)	418 (88%)	100 (000)			
Black - N (%)	42 (9%)	408 (86%)	392 (86%)		
Hispanic - N (%)		50 (11%)	41 (9%)		
Asian - N (%)	7 (1%)	9 (2%)	6 (1%)		
Other - N (%)	1 (<1%) 7 (1%)	0 (0%)	1 (<1%)		
Gender	7 (176)	6 (1%)	14 (3%)		
Female - N (%)	222 (708.)	00.1 (00.1)	1		
Male - N (%)	333 (70%) 143 (30%)	321 (68%)	306 (67%)		
Disease Duration - Years	143 (30%)	153 (32%)	148 (33%)		
Mean (Std. Dev.)	0.1 (9.43)	.			
Range	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)		
· · - · · 3 -	(b)(4)				
<5 years - N (%)	172 (36%)	158 (33%)	140 (220)		
≥5 years - N (%)	304 (64%)	316 (67%)	149 (33%) 305 (67%)		

Table A.4 WOMAC Index

How much pain do you have?

- walking on a flat surface
- going up or down stairs
- at night while in bed
- sitting or lying
- standing upright

Amount of joint stiffness

- How severe is your stiffness after first awakening in the morning?
- How severe is your stiffness after sitting, lying, or resting later in the day?

Ability to move around and to look after yourself - degree of difficulty

- descending stairs
- ascending stairs
- rising from sitting
- standing
- bending to floor
- walking on flat surface
- getting in/out of car
- going shopping
- putting on socks/stockings

- rising from bed
- taking off socks/stockings
- lying in bed
- getting in/out of bath
- sitting
- getting on/off toilet
 - heavy domestic duties
 - light domestic duties

Score: none, mild, moderate, severe, extreme

Table A.5: Osteoarthritis Severity Index (knee)

Inquiries Related to Pain	Points*
Nocturnal pain	
· none	0
only on movement or in certain positions	0 1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
· yes	1
Pain on walking	
- none	0
 only after walking some distance 	1
 very early after starting to walk and increasing 	2
Pain or discomfort when getting up from the sitting position	
· no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
 More than 1 km (0.62 miles), but limited 	ĭ
 About 1 km (0.62 miles, about 15 minutes) 	2
 From 500 to 900 m (547-985 yards, about 8-15 minutes) 	3
 From 300 to 500 m (328-547 yards) 	4
 From 100 to 300 m (109-328 yards) 	5
 Less than 100 m (109 yards) 	6
 With one walking stick or crutch 	+1
 With two walking sticks or crutches 	+2
Inquiries related to activities of daily living*	
 Can you go up a standard flight of stairs? 	0 to 2
 Can you go down a standard flight of stairs? 	0 to 2
- Can you squat completely?	0 to 2
- Can you walk on unever ground?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.6: Osteoarthritis Severity Index (hip)

Inquiries Related to Pain	Points*
Nocturnal pain	
· none	•
- only on movement or in certain positions	0
- without movement	1
	2
Duration of morning stiffness or pain after getting up	
- none	0
 less than 15 minutes 	1
15 minutes or more	2
Remaining standing for 30 minutes increases pain	
· no	0
- ves	1
Daniel H.	·
Pain on walking	
- none	0
 only after walking some distance 	1
 very early after starting to walk and increasing 	2
Pain or discomfort when getting up from the sitting position	
- no	0
· yes	1
Inquiries related to maximum walking distance	
Unlimited	0
- More than 1 km (0.62 miles), but limited	0
About 1 km (0.62 miles, about 15 minutes)	1 2
 From 500 to 900 m (547-985 yards, about 8-15 minutes) 	3
- From 300 to 500 m (328-547 yards)	3 4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
 With two walking sticks or crutches 	+2
Inquiries related to potivities of delicities	
Inquiries related to activities of daily living*	
- Can you put on socks by bending forward?	0 to 2
- Can you pick up an object from the floor?	0 to 2
- Can you go up a standard flight of stairs?	0 to 2
- Can you get into and out of a car? *Point Score: No difficulty = 0: Mitch difficulty = 1.	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.7.1 Physician's Global Assessment (Protocol 054)

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS PAST 1 OF 4: DESERVED MEANS (a) (b)

	IMMEDIM-TO-THEA	G COMORT (177)	•	
PLATESO	20-58635	CD-58635	# 0 × 5 5 5 2 2 1 1	
(M=217)	TUNG BID (N≈216)	0.04MW 800 0.04=0.070	200M/4 B15 1074213	
117	216	pag	213	
3.8				
0.60	0.60	0.56	3.5 0.40	
237	214	262		
			213	
5.45	0.83	0.81	2.5 3.57	
			· · ·	
217	5 - g	100 pts, max		
			213	
0.91	C.94		0.94	

212	53.5	0.00		
			313	
5.90	0.98	1.9 0.95	2.9 1.02	
	##=217) 117 3.8 0.60 217 3.2 3.2 3.91 217 3.2	PLATERO SC-58635 #M=317) FOMG BID #M=217) (N=216; 117 216	### 216	

⁽a) This (able is based to the last theervation carried forward approach (b) Scale ranged from 1 (very good) to 5 (very poor)

PRYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS FART COST OF CONTROL CHANGE ANALYSIS, NUMBER OF PATTERTS (%) (a)

INTENTHICHTS TARACTER

	F1ACERG (N=217)	SC-58635 SOMG BID (N=216)	SC-58635 186M3 BTD (N=207)	SC-58635 200MG Bib (N=313)	NAPROXEN 500MG EID (N=207)	LINEAR THEND D-VALUE (d)
WEEK 2 IMPROVED (b) NO CHANGE UORGENED (c)	37 (175) 172 (795) 8 (46)	55(25%) 158(73%) 3(1%)	60(29%) 145(704) 2(<1%)	69(32%) 140(56%) 4: 2%)	63 (30%) 141 (68%) 5 (1%)	40.001
TOTAL	217(100%)	316(100%)	207(100%)	1137(1002)	207(100%)	
WEST 6 IMPROVED (E) NO CHANGE WORSENED (C)	42 (196) 15% (76%) 9 (4%)	68 (31%) 144 (678) 41 - 25)	135(454)	80(38%) 129(30%) 8(20)	631 30%) 1391 67%) 51 2%)	∾∪.0⊽1
TOTAL	017716685	216(100%)	207:100%;	213(200%)	007(100%)	
WEER 12 IMPROVED (b) NO CHANGE SYPPENED (c)	200 1883 1887 1843 51 28	591 278) 1307 708) 57 28)	339: 67%)	63(30%) 345(88%) 51 2%)	66 (32%) 336 (66%) 5 (28)	9.502
TOTAL		200.2008)	21 = 111X+	217:100%)	292120945	

per CACURAL BURK TREATMENT OF METABLES TOS $\{(v_i)_{i=1}^{n}\}$

	F.I	245					NI ASYMMAN			
	VS. FLACEBO	V3. FLACEBI	TAME FILE	1318 - FID 27.	Olama Bir Na	Dina sin	124 PPI XEE!	NAPECKED	MARFINER	A1 6 T. P. C. L. C.
WEEK (C)	0.001*	40.001* 40.001* 0.000*	5.000 <0.000 0.004	7.747	1.213	3.283	.0.30. 0.013 <0.001	0.242 0.535 0.535		0.789 3.183 0.536

⁽a) This table is tased on the last inservinian diried forward approach.

(b) Imprived is defined as reduction of at least two grades from baseline for grades 1-5 or a change in grade from 2 to 1 co) Respond to defined to an increase of at least two grades from baseline for grades 1-5 or a change in grade from 4 to 1 to Contractly stell-hadded test of linear loss trend stratified by renter (Monzero Contract). Represent the contract of the contraction arranged by decree (Fig. Mean Montes Titler). Statistically significant alcording to the Author, provider (gridary pairwick comparisons only).

Table A.7.2 Physician's Global Assessment-continued (Protocol 054)

INTEND-TO-TREAT CONCRT (ITT)

			PLACE (Nali	5.5	1-58635 MG BIL NIIE	100	56635 MG 870	20	HO ETL	NAPPONEN 500MG BID	OVERALL p-VALUE:c.	DINEAR TREKU
						-,-			:	154F22.	p=tAluErd,	p-VALUE(d)
THEK 1											<7.001	an con
	MEAN, CHANGE		1.4		0.9	1	. 1		·	1		
OTO DEV			5.3		1.9-					2.47		
LS NEAL :	CHANGE (c)		-, f	-	6.9	1.0	1	-		1		
CEEF 6												
CECETATES	MEAN CHANCE		6		1.5		-				#2.191	<0.061
ATO DEV					1	:			1.30	1.7		
LE MEAN &	JEZNUE inch		1.5						1.1			
						•			2.2	1.1		
260. J.J.											<0.001	80.001
	MEAN CHAMBE		1.0		6.9	4	. 3		1.5	1 5		S 17 , 11/2 2
ATO LEY			1.3		11.64					1155		
I FOREST A	THANGE FOI		7.5			1				1.1		
	tit it i name											
********	TH 35: COMPA	- Marking Adviced	ALS (0):	50MC 51D	US. NAF	FALKELI		255.2	III VS. II	AFAGNEU	D(OMO BID (S. KAFROKEN
	536FF 21s			3.83 r s	6.90 tz	p 977		- 10			0.97 (0.8	
	WEEK 6:			0.99 /				153	4,85 (6		1.05 (0.8	
	PHDF 3.3:			0.91 (1 6 1 7 7 1 9		0.90 (0.7	
								*		* * * * *	2000 (000	2 (2 1.05)
> VALUES FO	OR TREATMENT	COMPARISONS	(1):									•
	PR	MARY	,				. .	. 17 W. 175	NTDA DAY			
	100MS PID	Secke bid	50MG BIT						NAPROXEN	NAPROXEN	NAPROXEN	MAPROXEN
	VS.	VS.	V5.	72.	V3		VS.		75.	VS.	VS.	
	PLACEBO	FLACERO	FLACESO	50293 BID	50 x G				FLACERO	10MS BID	100MG 8ID	
			~~~~~									200200 200
VEEK 2:		<0.09_*		0.031			3.8.5			0.019	0.850	0.671
		< 9.091	K61961	0.900	3.49				k0.301	0.925	0.981	0.555
WEEK 12:	<0.001*	<0.001*	+6.061	6.501	2.40	2	0.421	:	k9.601	0.298		0.245

[[]a, 3his table is based on the last observation carried toward appoint [6].

[b) Scale (anged from 1 (very good) to 5 (very poor) with negative charge indicating improvement [6]. From Analysis of Covariance model with treatment and center as functure and Baseline value as covariate, the corresponding BOOT MSE are: 0.796 for week 2, 0.892 for week 6, and 0.916 for week 12.

[6] From a contrast statement from Analysis of Covariance model in (c). Naproxem group was excluded [6] G-PATIO is defined as the ratio of least square mean changes from (c), of SC-55635 group versus Naproxem group [6] From a contrast statement from Analysis of Covariance model in (c)

* Statistically significant according to the Hochberg procedure (primury pairwise comparisons only)

## Table A.8.1 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS PART 1 OF 4: OBSERVED MEANS (a) (b)

#### INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-59635 50HG BID (N+216)	SC-58635 100M3 BID (N=207)	SC-58635 260H2 BID (N=213)	NATROXEN 500MS BID (N+107)
BASELINE					
n Mean Std dev	21? 3.e C.61	21€ 3.8 0.€4	267 3.9 8.61	213 4.0	207 3.9
		0,04	D. 61	0.59	0.54
WEEK 2					
N	217	216	207	213	207
MEAN	3.3	2.9	2.7	2.8	2.7
STD DEV	0.90	2.88	0.85	0.90	0.88
WEEK 6					
N	217	216	267		
MEAN	3,5	2.9	2.9	213	3.07
STE DEV	€.97	0.97	0.95	2.8 1.58	Z.8 2.61
WEEK 12					
Ħ	217	216	207	213	
MEAN	3.4	2.9	2.8		207
SIC DEV	0.96	1.01	1.53	3.0 1.09	2.5 2.06

⁽a) This table is based on the last observation carried forward approach

#### PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (R) (a)

#### INTENT-TO-THEAT COHORT (17T)

	FLACEBO	90-56635	90-58635	50-58635	NAPROXET:	LINEAR
		594G B1D	100MG BID	200MG BID	500MC EID	TREND
	(N=217)	(N=116)	N=2071	(N=213)	(N=207)	
			. 207.,	124-2237	(N=40)1	D-VALUE (d)
WEEK 2						
IMPROVED (b)	35 . 460 .					<0.001
	35( 16%)	51( 24%)	67 ( 32%)	75( 35%)	€6 ( 32%)	
NO CHANGE	171 ( 79%)	.160 ( 74%)	137 ( 66%)	132( 62%)	138 ( 67%)	
WORSELTED (c)	11(5%)	5 ( 2%)	3( 1%)	€( 3₺)	3( 1%)	
		-,,	20;	6 ( 35)	31 £6)	
TOTAL	217 (100%)	216(100%)				
	217(1005)	215(100%)	207 (106%)	213(100%)	207(1001)	
WEEK 6						
IMPROVED (b)						<0.001
	38( 18%)	67 ( 31%)	71 ( 34%)	78 (37%)	€3 ( 36%)	
NO CHANGE	162( 75%)	143 ( 65%)	131( 63%)	126( 59%)	139 ( 67%)	
WORSENED (c)	17 (8%)	6(3%)	5 ( 28)	9 ( 4%)	5( 2%)	
				31 461	2 ( 24)	
TOTAL	217 (100%)	216 (100%)	<b>***</b>			
	2271.0061	225(1005)	207 (100%)	213(100%)	207 (100 m)	
WEEK 12						
INPROVED (b)	30 31 1					0.001
	36 ( 174)	56 ( 268)	65( 31%)	61( 29%)	70 ( 34%)	
NO CHANGE	164( 76%)	153 ( 71%)	137( 66%)	242 ( 578)	131( 63%)	
WORSENED (c)	17 ( 8%)	7 ( 3%)	5(2%)	101 5%)	6: 3%1	
			- ( - ()	*41 -7	0: 361	
TATOT	217(100%)	216(1001)	207 (100%)	222/100		
			201(2006)	213(100%)	207/106%1	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY									
	100MG RID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	VS.	200MG BID VS.	200MG BID	NAPROXEN VS.	NAPROXEN VS. 50M3 BID	NAPROXEN VS.	NAPROXEN VS. 200MG BID
WEEK 2: WEEK 6: WEEK 12:	<0.031* <0.031* <0.001*	<0.001* <0.001* 6.007*	0.016 <0.001 0.004	0.044 0.543 0.256	0.017 C.423 0.794	0.427 0.402 0.606	<0.001 <0.001 <0.001	0.672 0.837 0.151	0.954 0.464 0.677	0.764 6.246 6.174

 ⁽b) Scale ranged from 1 (very good) to 5 (very poor)
 By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

⁽a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from baseline for grades 2-5 or a change in grade from 2 to 1
(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5
(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation), Magroxen group was excluded
(e) Cochran-Hantel-Haenszel test of treatment comparison stratified by center (Now Mean Socies Differ)

- Statistically significant according to the Northwest procedure (primary pairwise comparisons only)

## Table A.8.2 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (c)

#### INTENT-TO-TREAT (ITT)

	PLACESO	56MG	BID 100	G BID 1	COMS RID	NAPEONEN SORMU PID	OVERALL	LINEAR TWENT
	(N#217)	(M=21	6) (N=)	207) ((	N=213)	(M=207)	p=V&DMEter	
WEEK 2							<0.001	28 CC.
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.	. 2	-1.1	-1.7		-0.052
STD DEV	⊇.96	0.9.	20.	. 90	0.96	0.30	:	
LS MEAN CHADGE (5)	-0.€	-0.9	- 1 .	. 2		-1.1		
WEEK 6							e6.361	
OBSERVED MEAN CHANGE	- 5 . 5	0.5	-1	1	-1.1	-1 7	.0.01	V91,202
STO DEV	1 (3.1)	1.01	;	116	1 0.02	6 6 5		
LS MEAN CHANGE (c)	-1.£	-1.0	-1.	.1 -	1.1	-1.1		
WEEK 12							.0.021	6.44.
OBSERVED MEAN CHANGE	6,	O 6	- 1	,	-1.0	, ,	<0.001	* C. 35.1
STU DEV	1.00	1 04	· · ·	0.6	1.67	1 07		
LS MEAN CHANGE (c)	-0.5	-0.9	-1.	1 -	0.9	-1.1		
Q-RATIC WITH 95% CONFIDENCE INTERVALS	iei so	NAC BID DE	NADOOYER	1000		DE OMES	000000	_
		7. R. DID 13.	TOTA NONE	1001	: D.D (5. NO	AFFEARIN	ZUUMG BID V	S. NAPROXEN
WESK 2:	ō	0.78 L G.66	to 0 91)	0.93	1 2 2 85 FA	1 121	0.93 ( 0.8	1 671
WEEK €:	c	0.92 (0.72	to 1.10)	1 31	( 0 87 50	1.227	1.00 ( 0.8	2 [0 1,1,7]
WEEK 12:	C	0.82 ( 0. <b>€</b> 8	to 0.99	0.95	( 0.79 to	1.13)	C.83 ( 0.6	1 to 1.18) 3 to 1.39)
p-VALUES FOR TREATMENT COMPARESONS (£	h •							
PREMARY				SECC	NDARY			
100MG BID 100MG BIS 50	MG PID 10	CMG BID 2	DOMG BID	200MG BID	NAPROXEN	NAPROVEN	REPROVES:	TEDERVES:
vs. vs.	VB.	VS.	VS.	V⊆	ye	1/7	v.c	17.0
PLACEBO PLACEBO PL	ACEBO 50	MG BID 5	OMG BID	100MG BID	PLACEBO	50MG EID	100mg Fib	100MG BID
WEEK 2: <0.000 € <0.001 € <0.001 €	0.01	2004	5 656			0.001		
WEEK 6: <0.001* <0.001* <0.001* <0.001* <0.001* <0.001* <0.001* <0.001* <0.001*								
	.001 0	.273	0.375	0.832	<0.001	0.356	0.859	0.073

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.625 for week 2, 0.941 for week 6, and 0.967 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of 50-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)

Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

## Table A.9.1 Patient's Assessment of Arthritis Pain (protocol 020)

		INTENT-TO-TREA	T COHORT (ITT) .		
	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN
	(N=203)	(N=203)	(ボ=197)	(N=202)	500MG BID (N=198)
BASELINE					
M	201	203	196	201	197
MEAN	69.4	66.9	66.0	68.9	71.4
STD DEV	17.13	10.13	16.17	15.43	14.97
WEEK 2					
N	201	203	196	201	197
MEAN	56.1	49.2	41.9	44.0	42.2
STD DEV	26.24	25.53	25.77	24.96	26.52
WEEK 6					
N	201	203	196	201	107
MEAN	51.1	49.3	41.6	43.8	197
STD DEV	29.04	26.83	27.84	27,05	41.9 29.07
WEEK 12				•	
N	201	203	196	201	
MEAN	52.7	50.9	43.8		197
STD DEV	29.41	28.29	26.05	45.5 29.23	45.8 29.29

⁽a) This table is based on the last observation carried forward approach

# TABLE 18 PATIENT'S ASSESSMENT OF ARTERITIS PAIN (VAS) PART 2 OF 3: MEAN CHANGE AMALYSIS (a) (b)

#### INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BIE (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID	OVERALL	LINEAR TREND
	(4-205)	(M-203)	(M-13/)	(M=202)	(N=198)	p-VALUE(c)	p-value(d)
WEEK 2						<0.001	<0.001
OBSERVED HEAR CHANGE	-13.3	-17.7	-26.1	-24.9	-29.2	.0.001	VU. UUI
STD DEV	23.28	25,99	26.19	24.81	26.88		
LS NEAN CHANGE (c)	-12.1	-18.4	-26,1	-24.6	-27.3		
WEEK 6						<0.001	<0.001
OBSERVED NEAN CHANGE	-18.3	-17.7	-26.4	-25.1	-29.5	-0.001	.0.001
STD DEV	27.38	29.22	27.76	26.40	30.28		
LS NEAN CHANGE (c)	-16.6	-17.9	-25.9	-24.5	-27.0		
WEEK 12						0.002	<0.001
OBSERVED NEAN CHANGE	-16.7	-16.0	-24.1	-23.3	-25.6	0.002	
STD DEV	29.05	29.81	27.31	29.18	29.14		
LS NEAM CHANGE (C)	-15.1	-16.0	-23.1	-22.1	-22.7		
Q-RATIO WITH 95% CONFIDENCE INTERVAL	S (e): 50M	G BID VS. NAP	ROXEN	100MG BID VE.	NAPROXEN	200MG BID 1	S. NAPROXEN
WEEK 2:	0.	67 ( 0.53 to	0.84)	0.96 ( 0.80 (	0 1 151	0 90 ( 0 -	4 to 1.09)
WEEK 6:		66 ( 0.51 to		0.96 ( 0.78 )			4 to 1.12)
WEEK 12:		70 ( 0.51 to		1.02 ( 0.80			6 to 1.25)

#### p-VALUES FOR TREATMENT COMPARISONS (f):

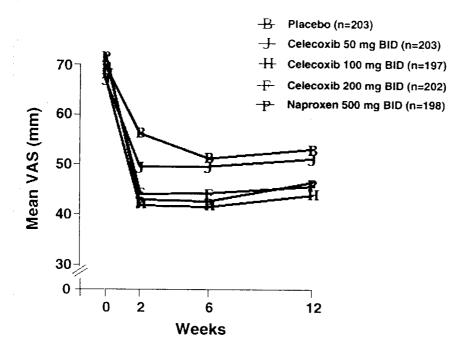
	PRI	MARY				SECO	MDARY			
	100MG BID VS. PLACEBO	VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID V8. 50MG DID	200MG BID VS. 100MG BID	VS.	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100NG BID	NAPROXEN VS. 200NG BID
WEEK 2: WEEK 6: WEEK 12:	<0.001* <0.001* 0.003*	<0.001* 0.003* 0.009*	0.009 0.628 0.735	0.001 0.002 0.008	0.010 0.013 0.023	0.514 0.579 0.701	<0.001 <0.001 0.005	<0.001 <0.001 0.014	0.643 0.700 0.875	0.263 0.346 0.822

⁽b) Scale ranged from 0 to 100 (mm) with lower score as better

* By definition, in this and subsequent efficacy tables, the ITT cobort includes only knee patients who had at least one dose of study medication

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate,
the corresponding ROOT MSE are: 23.93 for week 2, 26.22 for week 6, and 27.02 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Reproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group varsus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Nochberg procedure (primary pairwise comparisons only)

Table/Figure A.9.2 Patient's Assessment of Arthritis Pain (020)



## Table A.10.1 Patient's Assessment of Arthritis Pain (protocol 054)

TABLE 18

PATIENT'S ASSESSMENT OF ARTHRITIS FAIN (VAS: PART 1 OF 3: OBSERVE) MEAUE (A 1 A)

		intent-to-tab	AT COMUNET FITT.		•
	PLACEBO	50 (55635 50 <del>8</del> 0 210	50 58635 100 <b>M</b> 0 Bin	SC-58635	MARF. NEX
	(N+217)	8-216	N-227	100m0 BID (N=213)	50.0%0 F21 (N=200
BASELINE					
N	2:5	214	247	212	26"
MEAN	#8 II	4, 4	15.1	67.6	67 -
STD DEV	14,67	16.12	16.99	15.69	16.47
WEEK 2					
н	217	1.5	2.37	213	207
MEAN	57.0	4 % . 4	43.7	44.2	42.:
NEG OLIG	24.68	25.97	26,09	27.11	25.14
WEEK 6					
11	217	210	207	213	267
MEAN	55.6	45.0	43.0	44.9	4 1
STD DEV	26.11	2P.15	27.33	29.65	**. 20.11
WEEK 12					
Ħ	217	216	207	213	**
MEAN	57.4	50.0	44.6	49.0	
STD DEV	25.71	28.69	29,13	28.89	\$ 2. :
				20.59	37.12

⁽a) This table is based on the last observation carried forward approach

# TABLE 18 PATIENT'S ASSESSMENT OF ARTHEITIS PAIN (VAS) FART 2 CH 3. NEAR CHANGE ARRALYSIS (a) (b)

INTENDED: FEBAT CHECET (CTT) 80 58635 - 00 58625 100M0 BID - 188M6 BID 6N-2000 - (M-013) NAPFOXER LINEAS 50 MOVEMENTS OVEFALL TREND p-VALUE(c) p-VALUE(d) 10-211 11.8 13.62 -11.8 OBSERVED MEAN CHARGE -19.3 -24.67 -19.7 STD DEV LS NEAN CHANGE (-) 25.40 OPSERVED MEAN CHANGE -12.6 25.31 -13.2 -20.9 -27.04 -21.5 -04.2 26.97 -25.1 STD DEV LS MEAN CHANGE (c) 28.87 -23.9 OBSERVED MEAN CHANGE 18.7 38.24 -19.0 STO DEV LS MEAN CHANGE (c) 28.67 -19.3 -23.3 Q-RATIO WITH 95% CONFIDENCE INTERVALS (e): SOMO EIL VS. NAFROXEN 109MG BID VS. NAFROXEN 200MS BIE VS. MAFROXEN WEEP 0: 0.74 1 0 60 to 0.918 9.89 1 0.69 to 1.089 0.85 | 0.66 to 1.101 0.90 ( 0.76 pc 1.10) 0.92 ( 0.70 c) | 110; 6.96 ( 6.76 t) | 1119; 6.87 ( 6.67 t) | 1110; 1.01 ( 0.82 to 1.24) 1.05 : 0.83 to 1.32) WEEK 12:

p-VASCES FOR TREATMENT COMPARISONS of a

	PR3	MARY :				SEC1	NIMFY		<b></b>	
	100MG BID VS.	COCMU BIC Ma.	SIMS FID VS.	.16ma ett va. Suma ett	191 <b>M</b> 9 EID VS.	200 <b>M3</b> BID UZ.	NAPPOXEN VE.	NAPEOXEN VS.	NAPROXEN	M4790 (98)
WEEK G:	<0.001*	<\$1.14	40.171	2 739	0.323	6.9+0 e3^	40.191 40.131	. 003	0.250 6.250	1.362
MEER 13:	<0.001°	6.511*	5.302	1 1.1		1.123			3.6%	0.757

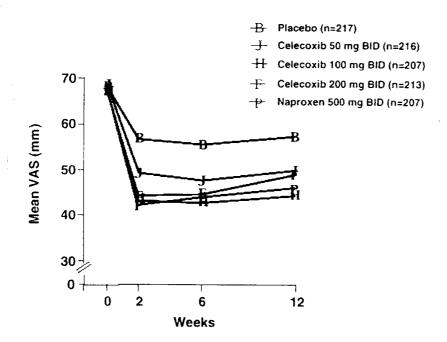
⁽b) Scale ranged from 6 to 190 (mm) with lower score as better

Tail this table is based on the last observation carried forward approach

b. Scale langed from 6 to 100 km. With negative change indicating hips weren.

c) From Acalysis of Organizate model with treatment and menter and factors and Papeline value as covar ate, the corresponding POOT ACE ater 10 00 for event 0 00 00 km at 20.00 for wheel 0 00 different actions and statement from Acalysis of Organizate Poot 20 contains total wheel for Acalysis of Organizate Poot 20 contains at a terminal of I can according to the Contains and contains the proof of the Contains the Contains that when the Radiation of Organizate Poot 20 contains the Contains the Contains and contains the Contains that when the Contains according to the Poot 20 contains the Contains that we have the Contains and contains the Contains that Contains the Contains th

# Table/Figure A.10.2 Patient's Assessment of Arthritis Pain (054)



### Table A.11 WOMAC pain (protocol 054)

SC-58635 COMFAFACTIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP OA E49-96-02-054

TABLE 21.1 NOMAT FAIR
PART 1 OF 2: OBJESTED MEANS (a) (E)

INTENT: TO: TREAT CORORT -171.

	PLACEBO	50-58635 50M0 BID	50-58615 100MG Rin	SC-58635 27689 BID	NAPROXEN 500MG BID
	(N=2.17)	ON=016.	[M=107]	(N=212)	(N=267)
EASIELINE					
1;	217	215	217	311	207
HEAH	19.6	10.5	le.⊬	10.8	
STC DEV	3.25	1.4	8.33	2.95	10.5 3.54
WEEK 2				*	
н	217	2.6	207	212	237
MEAN	10.0	8.*	E.1	8.3	7.4
STD DEV	3.66	5.85	3.62	3.57	3.74
WEEK 12					
· N	217	216	267	213	0.7.5
MEAN	9.7	9.0	8.5	8.5	207
STD DEV	3.98	3.99	4.22	4.20	8.0 3.94

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 20 with lower score as better

#### INTENT-TO-TREAT COHORT (ITT)

			PLACI (N=2)	50 <b>M</b> :	S BIC 1	30MG RID	SC-58635 200MG BID (N=213)	NAPROXEN 500mg BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2 OBSERVED SID DEV LS MEAN C	MEAN CHANGE HANGE (c)		- 6 . 8 3 . 3 - 6 . 1	59 3.	.30	-2.5 3.26 -2.6	72.5 13.27 -2.5	-2.7 3.20 -2.9	<0.001	r0.001
HEEK 12 OBSERVED STO DEV LS MEAN C	MEAN CHANGE HANGE (C)		- 0 . 3 3 . <del>-</del> - 1 . 3	in 3.	41		-2.4 3.91 -2.4	-2.5 3.61 -2.7	<0.001	<0.001
p-VALUES FO	e treaiment	COMFARISONS	(e);							
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG RII VS. 50MG FID	0 000MG BI VS. 100MG BI	VS. D FLACEBO	DAPPOXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAFROKEN VS. 200MG BID
WEEK 3: WEEK 13:			<0.001 0.034	0.004	0.009	0.804 0.607	<0.001 <0.001	<0.001 41.002	0.394 0.179	0.271 0.403

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxem group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

# Table A.12 WOMAC pain (protocol 020)

TABLE 21.1 WOMAC PAIN FART 1 OF 0: ORSERVED MEANS (a) (b)

INTENDED. TO THEAT CLEOF FOR THE PATIENTS ONLY

	PLACEST	00-55035 50M0 Bib 804003	ST-58635 100MG BIT (N=187)	SC~58635 200MG BID (N≃202)	NAPROXEN 500MG BID (N=198)
BASELINE					
ři	271	157	196	201	198
MEAN	11.5	17.7	10.5	10.7	11.0
STE DEV	3.41	3.18	3.36	3.36	2.97
WEEK 3					
N	201	197	196	261	198
MEDAN	10.0	8.7	7.€	5.9	8,2
STE DEV	3,99	3,77	3.75	3.80	4.00
WEER 11				•	
27	201	197	196	201	198
MEAN	9.4	8.6	7.4	7.9	277 3.4
STD DEV	4.43	4.39	4.17	4.19	4.25

(a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 20 with lower score as better

STO DEV	MEAN CHANGE HASSE (c)		2.9	۴ ۹	.15	3.29	-1,9 3,58 -2,8	3.85	<0.001	
ero dev	MEAN CHANGE HANGE (c)		:1. <b>4</b> 3.8 -1.2	4 3	59			-2.6 3.91 -2.4	<0.901	<0.901
p-Values fo	R TREATMENT	COMPARISONS	(e):							
	vs.	200MG B10 V3. PLACEBO	56MG BID V3 PLACEBO	100MG BIL VS. 50MG BID	2.0mg bib VS. 50mg Alb	200MG B18 VS. 100MG BII	vs.	NAPROXEE VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEM VS. 166MG BID
WEEK 2:	<0.001	×0.061			0.010	0.520	<0.001	0.024	0.340	0.751

⁽a) This table is based on the last observation parried forward approach
(b) Scale ranged from 0 to 00 with negative change indicating improvement
(c) From Analysis of Covariance model with creatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

### Table A.13 WOMAC stiffness (protocol 054)

TABLE 21.2

WOMAC JOINT STIFFNESS
FART 1 OF 2: OBSERVED NEARS (a) (b)

		intent-to-tre	AT COHORT (ITT)		
	PLACEST	SC-58695 50MG-81D	50-58635 100 <b>m</b> G BID	SC-58635 200MG BID	NAPROXEN 500MG BID
	(N=217)	(N=216)	(N=267)	(N=213)	(K=207)
BASELINE					
N	217	016	207 .	211	205
MEAN	4.6	4.7	4.6	4.7	4.6
STD DEV	1.42	1,48	1.54	1.40	1.60
WEER 2				•	
);	217	216	267	212	207
MEAN	4.4	4.0	3.7	3.7	3.6
SID DEV	1.49	1.57	1.60	1,62	1.63
WEEK 12					
N	217	216	207	213	207
MEAN	4.3	3.9	3.7	3.7	3.6
STD DEV	1.59	1.61	1.77	1.68	1.64

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 8 with lower scare as better

#### INTENT-TO-TREAT COMORT (ITT)

	PLACEBT (N=217)	EC-58635 50MG BID (N=116)	5C~58635 100MG BID (N≈207)	SC~58635 200MG_BID (N=213)	NAPROXEN 500MG EID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d
VEEK 2						<0.001	∢0.001
OBSERVED MEAN CHANGE	-0.3	-0.8	-1.0	-1.0	-1.0		
STD DEV	1.37	1.45	1.59	,1.56	1.54		
LS MEAN CHANGE (c)	-0.3	-0.8	-1.0	-1.0	-1.1		
VEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.3	-0.8	-G.9	-1.0	-1.0		
STD DEV	1.61	1.50	1.67	1.75	1.56		
LS MEAN CHANGE (c)	-9,4	-0.8	-1.0	-1.0	-1.1		
-VALUES FOR TREATMENT COMPARISONS	(e):						
100MG BID 200MG BID	50MG BID 100	4G 5ID 200MG	BID 200MG	BID NAPROXE	NAPROXEN	NAPROXEN	NAPROXEN

	vs.	VS.	ys.	75.	VS.	VS.	V۵.	vs.	VS.	VS.
	PLACEBO	PLACEBU	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	106MG BID	200MG BID
WEEK 2:	<0.001	<0.001	<0.001	3.044	0.031	9.895	<0.001	0.007	5.498	0.564
WEEK 12:	<0.001	<0.001	0.064	0.148	0.132	0.959	<0.001	0.017	0.354	0.379

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 0 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

## Table A.14 WOMAC stiffness (protocol 020)

TABLE 21.2

WOMAC JOINT STIFFNESS

PART 1 OF 2: CESERVED MEANS (a) (b)

### INTENT-TO-TREAT COBORT (ITT) - KNEE PATIFIXIS CNLY

	PLACESO (N=2 )3:	SC-58635 50MG EID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPRJKEN 800MD BID (Na19A)
NASELINE N MEAN STD DEV	202 4.9 1.35	197 4 A 1,21	196 4.7 1.47	201 4.9 1.50	195 9.0 1.40
HEEK 2 N MEAN STD DEV	202 4.5 3.59	197   d v <del>1</del>   4 v <b>4</b>	196 1.5 1.65	291 3.6 1.62	195 3.7 1.69
MEEK 12 MEAN SID DEV	202 4.3 1.72	107 3.9 1.73	196 3.5 1.71	201 3.7 1.69	195 3.7 1.81

⁽a) This table is based on the last observation carried forward approach(b) Scale ranged from 0 to 8 with lower score as better

#### INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203,	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=1971	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2 OBSERVED MEAN CHANGE STD DEV LS MEAN CHANGE (c)	-8.4 1.33 -8.3	-0.9 1.49 -0.9	-1.2 1.58 -1.2	-1.3 1.66 -1.3	-1.3 1.83 -1.1	<0.961	<0.001
DESERVED MEAD CHANGE STD DBY LS MEAN CHANGE (C)	-6.6 1.61 -0.5	-0.9 1.60 -0.9	-1.2 1.57 -1.2	-1.2 -1.71 -1.1	-1.2 1.90 -1.1	<0.001	<0.001

#### p-VALUES FOR TREATMENT COMPARISONS (a):

	160MG SIC VA. PLACERO	200MG BID VS. PLACEBO	50MG BID VG. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	ys.	NAPROXEN VS. 50MG BTD	NAPROXEN VS. 100MG BID	NAPROXEN VS. 300MG BID	
WEEK 2: WEEK 12:	<0.001 <0.001	<0.001 <0.001	40.001 0.013	0.019 0.026	0.027 0.149	0.674	<0.001 <0.001	0.091	0.510 0.446	0.613 0.995	

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 3 to 8 with negative change indicating improvement
(c) From Analysis of Covariance model with freethent and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

### Table A.15 WOMAC function (protocol 054)

TABLE 71.3 WOMAN FRIBICAL FUNCTIONING PART 1 NF 2: OPDERVED MEANS (a) (b)

INTENT TU-TREAT CLEUPT (ITT)

		18.28. 19.18	:Na:::::::::::::::::::::::::::::::::		
	FLACEF D	50-55135 56M2 BIL	90-58635 101M0- <b>81</b> 0	GC-58635 100MN BID	NAPROKEN 500MG BID
	(N=217)	Na 2 1 5	. N≠2.1™:	(0*213)	(K=207)
BASELINE					
N	217		257	211	307
MEAI:	35.5	34 1	04.9	35.4	34.7
STE BEV	11.30	12.29	12 14	11.13 ,	10.01
WEEK 2					
N	217	215	307	212	207
MEAN	33.3	29.2	27.2	27.6	26.5
STE DEV	12.60	12.73	13.32	12.71 '	12.43
WEEK 12					
N	217	215	26"	213	247
MEAN	32.5	29.3	28.2	26.2	76.E
STD DEV	12.99	13.64	14.75	13.79	13.23

(a) This table is based on the last observation carried forward approach (b) Scule ranged from 0 to 68 with lower score as better

#### INTENT-TO-TREAT COBORT (ITT)

	PLAJEBY (N=217)	SC-58835 50MG BID (N=216)	SC-58635 100MG BLD (N=107)	SC-58635 200MG RID (N=213)	NAPROXEN 500MG BID (N=207)	OVEFALL p=VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK I ORGERVED MEAN CHANGE STD DEV LS MEAN CHANGE (d)	-2.3 9.28 -2.3	-4.9 10.36 -5.4	-7.7 16.11 -8.0	.7.9 10.72 -8.1	-8.2 9.96 -8.7	<0.001	<0.001
WEEK 12 OBSERVED MEAN CHANGE STO DEV LS MEAN CHANGE (C)	-3.0 10.94 -3.2	-4.8 10.91 -5.5	-6.7 11.17 -7.0	-7.3 32.28 -7.5	-7.9 11.04 -8.4	<0.001	HU.901

p-values for treatment comparisons (e):

	100MG BID VS. PLACEBO	V3. PLACERO	SOMG BID US. PLACEBO	100MG EID VS. 50MG B1D	200MQ BID VS. 59MG BID	VS. 100MG BID	vs.	VS. 56MG BID	VS.	NAPROXEN V3. 200MG BID
	PDAGEBO	PERCEPO		3036 676		10083 212				
WEEK 2: WEEK 12:	<0.001 <0.001	<0.001 <0.001	<0.101 0.023	0.005 0.142	0.004 0.047	0.945	<0.001 <0.001	<0.001 0.004	0.470 0.160	0.511 0.369

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast systement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

### **Table A.16 WOMAC function (protocol 020)**

INTENTATOATREA	T COHORT	(ITT) ·	- KNEF	PATTEMES	CNIV

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500 MG BID
	(N=203)	(N=203)	(N=197)	(N=202)	(N=198)
BASELINE					
N	184	174	176	181	180
MEAN	36.0	3€.2	35.4	35.3	36.6
STD DEV	10.83	10.76	11.77	12.29	10.58
WEEK 3					
n	164	174	176	181	180
MEAN	35.0	29.3	26,2	26.9	28.1
SID DEV	13.52	13.06	12.88	12.94	13.23
WEEK 12					
. 31	184	174	176	181	180
MEAN	31.7	29.4	26,1	27,4	18.5
SID DEV	13.94	14.09	14.38	14.20	14.92

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 68 with lower score as better

# TABLE 21.3 WOMAN PHYSICAL FUNCTIONING FART 2 OF Z: MEAN CHANGE ANALYSIS (a) (b)

#### INTENT-TO-TREAT COHOFT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (M=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MC BID (N=198)	OVERALL p-VALUE(⊂)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
DESERVED MEAN CHANGE	-2.9	-€.9	-9.1	~8.4	- 8.5		
STD DEV	9.32	9.85	11.19	11.39	12.53		
LS MEAN CHANGE (c)	-2.6	-6.8	-9.3	-A.5	-8.3		
WEEK 12				· P		<0.001	<0.001
: ORSERVED MEAN CHANGE	~4.3	-6.8	-9.2	-7.9	-8.1		
STD DEV	11.21	11.61	12.26	12.62	13.23		
LS MEAN CHANGE (c)	-3.9	-6.8	-9.5	-a.1	-7.8		

#### p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID	200MG B10	50MG BID	100MG BID	200MG BID	200MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN
	VS.	VS.	VS.	VS.	VS.	vs.	VS.	VS.	VS.	VS.
	PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID
				*****						
WEEK 2:	<0.001	<0.001	40.001	0.021	0.113	0.460	<0.001	0.257	0.233	0.647
WEEK 12:	<0.001	<0.001	0.018	0.033	0.301	0.265	0.001	0.438	0.170	0.794

⁽a) This table is based on the last observation catried forward approach
(b) Scale ranged from 0 to 68 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and denter as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

### Table A.17 WOMAC composite (protocol 054)

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 1 OF 2: OBSERVED MEANS (a) (b)

#### INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 59Mg BID (N+216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213).	NAFFORED: SCHEG BID - N=187)
			23		23
BASELINE					
N	<u>\$2.7</u>	214	267	211	205
MEAN	59.7	49.3	58.2	50.9	49.≤
STD DEV	14.98	16 17	16 06	14.33	16.65
JEEK 2					
N	517	115	20*	212	257
MELAN	47.7	42.30	.y.o	39.6	37.9
STE DEV	16.85	17.40	17.80	17.69	16.98
SEEK 10				,	
N	217	215	207	713	227
MEAN	46.5	42.2	40.4	40.3	38.4
STD DEV	17.6R	18.66	19.99	18.92	17.97

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 96 with lower score as better

### WOMAC COMEDSITE SCORE PART 2 CF 2: HEAN CHANGE ANALYSIS (a) (b)

#### INTENT-TO-TREAT COHORT (ITT)

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500HG BID	OVERALL.	LINEAR TREND
	(N=217)	M=216)	(N=207)	(N=213)	(N=207)	p-VALUE (c)	p-VALUE(d)
WHEN 2						<0.001	< 6.001
OBSERVED MEAN CHANGE	-3.1	-7.3	-11.2	-11.4	-12.0		
STD DEV	12.59	13.97	13.91	14.72	19.74		
LS MEAN CHANGE (c)	-3.4	-8.0	-11.7	-11.7	-11.7		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	~4.2	-7.2	-9.7	-10.€	-11.5		
STO DEV	15.07	14.73	15.2H	16.83	15.43		
LG MEAN CHANGE (c)	-4.6	-8,0	-10.3	-11.0	-12.4		

p-valued for treatment comparisons (e):

	100MS BID VE. PLACEED	206MG BID Vs. PLACEBO	50MG BID VS. PLACEBO	100MG FID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	VS.	NAPROXEN VS. 50MG BID	NAPROXEN VS. 199MG BID	NAPROMEN VS. 200kg bid
WEEK 2: WEEK 12:	<0.001 <0.001	<0.001 <0.001	<0.201 0.014	1.003	6.063 0.036	0.985 0.613	<0.001 <0.001	<0.001 6.002	0.393	0.402 0.325

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

### Table A.18 WOMAC composite (protocol 020)

TABLE 21.4

WOMAC TOMECOITE SCORE

TAPT 1 OF 1: DECERVED MEANS (6) (b)

INTENT-TO-TREAT COHORT (III) - KNEW PATIENTS ONLY

	FLATEBO	\$0-57635 50MR BID	2C+58635 16CMG BID	SC-58635 200MG BID	NAPROXEN 500MG BIC
	(N=203)	%×103,	N=197)	(N=202)	(N=198)
EASELINE					
N	1.82	174	175	161	1.77
MEAN	51.6	51.8	<b>e</b> 7.5	53.C	52.9
STD DEV	14.86	14.35	15.67	16.36	13.97
WEEK 2				•	
N	1.62	174	175	191	127
MEAN	47.5	42.1	37.4	36.5	40.2
ETD DEV	17.34	17.68	17.44	17.69	18.50
WEEK 12					
ĸ	182	174	195	191	177
MEAN	45.5	40.3	37.2	39.0	41.0
STD DEV	19.32	19.29	19.46	19.31	20.69

(a) This table is based on the last observation carried forward approach(b) Scale ranged from 0 to 96 with lower score as better

# TABLE 21.4 SOMEC COMPOSITE SCORE FART 2 OF 2: MEAN CHARGE ANALYSIS (A) (b)

INTENT-10-THEAT CLRUFT (ITT) - KNEE PATIENTS ONLY

	FIA-1663 (N-203)	AC 586+5 53M3 BIU (2842C3)	ST SEGSE TRENCE THE SEGSE	50-58635 200MG B1D (5=232)	(N=198) SOOMS RID NAPROXEN	GVERALL p=VALUE(c)	linear Trand p-value(d)
REEK 3 OBSERVED MEAN CHANGE STD DEV LS MEAN CHANGE (c)	^4 .1 12 .55 -2 .6	-9.7 13.52 -9.7	-13.1 14.91 -13.4	-12.5 -15.76 -12.5	-12.7 17.19 -11.9	<0.001	<0.001
REEK 12 OBSERVED MEAN CHANGE STO DEV LS MEAN CHANGE (c)	-6.1 15.58 -5.6	-9.5 15.76 -9.6	~13.3 16.40 ~13.6	-12.0 17.45 -12.1	~11.9 18.19 -11.3	<0.001	<0.001

#### p-values for treatment comparisons (e):

	100M3 RID VS. PLACEBO	200MG BID VS. FLACEFO	Vs.	100MG BID VS. 50MG PID	VS.	VS.	VS.	VS.	NAPROXED VS. 100MG BID	NAPROKEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	40.001	0.015	U.051	0.5 <b>4</b> 9	<0.001	0.137	0.296	0.650
WEEK 12:	<0.001	<0.001	0.016	0.019	U.146	0.3 <b>54</b>	<0.001	0.315		0.655

⁽a) This table is based on the last diservation carried forward approach
(b) Scale ranged from 0 to 96 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Paseline value as covariate
(c) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c).

### Table A.19 Withdrawal due to lack of Arthritis Efficacy (020, 054)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN OA M49-96-02-020

#### TABLE 22

INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

#### INTERT-TO-TREAT CORORT (ITT)

				PLACEBO (N-203)	501	-\$8635 eg Bid •203)	SC-58635 100MG BII (N=197)	2001	58635 MG BID 202)	NAPROXEN 500MG BID (N=198)
NUMBER WITHE ARTHRITIS EF		D LACK OF		79 (39%)	61	(30%)	40(20%)	49 (:	24%)	52(26%)
p-values for										
p-VALUES FOR	TREATMENT	COMPARISONS	(c):							
	50MG BID V9. PLACEBO	100MG BID VS. PLACEBO 	200MG BID VS. PLACEBO 0.002	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	WAPROXEN V5. PLACEBO	VS. 50MG BID	VS. 100MG BID	WAPROXEN VS. 200MG BID 0.647

(a) Fisher's Exact test for all five treatment groups
(b) Cochran-Mantel-Haenszel test of linear dose trend (Nonzero Correlation), Naproxen group was excluded
(c) Pairwise Fisher's Exact test

SC-5R635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP GA N49-96-02-054

### INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTERITIS EFFICACY

#### INTENT-TO-TREAT COHORT (ITT)

				FLACEBO		58635 G BID	SC-56635 100MG BID		8635 IG BID	NAFROXEN 500MG BID
				(N=217)	(N=	21€)	(N=207)	(N=2	(13)	(N=207)
NUMBER WITHDE ARTHRITIS EFF		LACK OF		112 (52%)	76	(35%)	61 (29%)	55 (	26%)	51 (25%)
p-VALUES FOR	OVERALS CO	MEARISONS (	a): <0.001							
p-VALUE FOR B	LINEAR TREM	ID TEST (b):	<0.001							
p-VALUES FOR	TREATMENT	COMPARISONS	(c):							
	SOMS BID MAI PLANEBA	100MG BID VS. FLACEEL	200MG BID VS. PLACEBO	100MG BID VS. SOME BID	200NG BID VS. SOMG BID	200MG SID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROKEN VS. 50MG BID	NAPROXEN VS. 1009KG PID	NAPROXEN VS. DOONG BID
	061	<0.061	<3.361	0.214	a.637	6.445	<0.001	0.020	0.319	0.515

⁽a) Finher's Exact tent for al. five treatment groups
(i) Cichion Mintel-Haenshel test of lines; isse trend (Nonzero Correlation), Naproxen group was excluded
(i) Pairwise Fisher's Exact test

## Table A.20 Time to Withdrawal-Lack of Arthritis Efficacy (054)

#### TABLE 23 TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY INTENT-TO-TREAT COHORT (ITT)

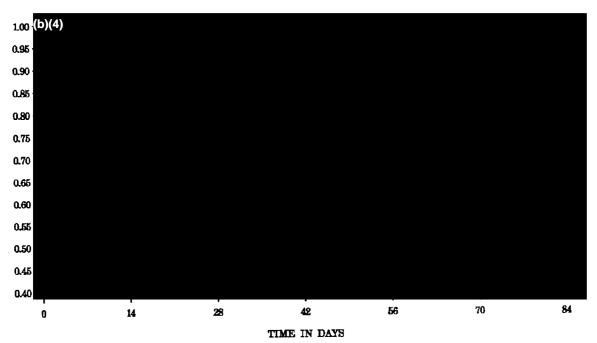


TABLE 23 TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY PART 5 OF V: LYV-FANE TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACE

INTENT-TG-TREAT COHORT (ITT)

0.544

<0.001

p-VALUE FOR OVERALL COMPARISONS (a : ₹0.001 p-VALUES FOR TREATMENT COMPASSIONS (D): 
 56MG BID
 100MG BID
 200MG BID
 200MG BID
 200MG BID
 COMD BID
 NAFROXEN
 VS. PLACEBO 0.363 8.024

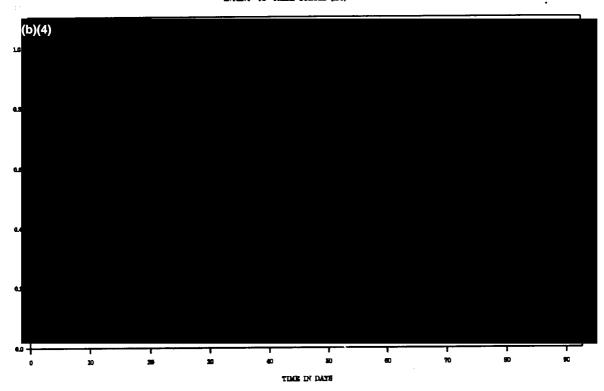
3.04€

(a) From log rank test for all five treatment groups (b) From pairwise Italiana .com

### Table A.21 Time to Withdrawal-Lack of Arthritis Efficacy (020)

TABLE SI
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS RIFICACY PART 1 OF 2: MAPLAN - MRIER ESTIMATES OF PROPOSITION OF PATIENTS WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)



SC-58635 COMPARATIVE EFFICACY AND SAFETY VS MAPROXEM IN OA M49-96-02-020

TABLE 23

TIME TO WITEDRANGL DUE TO LACK OF ARTERITIS EFFICACY

PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITEDRANGL DUE TO LACK OF ARTERITIS EFFICACY

INTENT-TO-TREAT COMORT (ITT)

p-value for overall comparisons (a):

<0.001

p-values for treatment comparisons (b):

50MG BID	100MG BID	200MG BID	100MG BID	200MG BID	200MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN
VS.	VS.	VS.	VS.	VS.	VS.	VS.	Vs.	V6.	VS.
PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID
0.017	<0.001	<0.001	0.065	0.142	0.648	0.002	0.420	0.295	0.530

⁽a) From log-rank test for all five treatment groups
(b) From pairwise log-rank test

## Table A.22.1 Reasons for Study Termination (020, 021, 054)

	Numbe	lumber of Osteoarthritis Patients by Treatment Group									
		Celecoxib									
Study	Placebo	50 mg BID	100 mg BID	200 mg BID	500 mg BID						
Study 020 *	(n≖204 ^t )	(n=203)	(n=197)	(∩≃202)	(n=198)						
Total Completed	91 (45%)	118 (58%)	116 (59%)	129 (64%)	116 (59%)						
Total Withdrawn	113 (55%)	85 (42%)	81 (41%)	73 (36%)	82 (41%)						
Lost to Foliow-up	3 (1%)	1 (<1%)	3 (2%)	1 (<1%)	3 (2%)						
Pre-Existing Violation	3 (1%)	1 (<1%)	0 ( 0%)	0 (0%)	1 (<1%)						
Protocol Non-Compliance	12 ( 6%)	4 ( 2%)	7 (4%)	2 (<1%)	8 (4%)						
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)						
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 ( 9%)						
Study 021 *	(n=242)	(n=252)	(n=240 )	(n=233)	(n=226)						
Total Completed	119 (49%)	168 (67%)	165 (69%)	154 (66%)	147 (65%)						
Total Withdrawn	123 (51%)	84 (33%)	75 (31%)	79 (34%)	79 (35%)						
Lost to Follow-up	5 (2%)	1 (<1%)	0 ( 0%)	2 (<1%)	1 (<1%)						
Pre-Existing Violation	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0 ( 0%)						
Protocol Non-Compliance	13 ( 5%)	8 ( 3%)	7 (3%)	4 ( 2%)	8 (4%)						
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)						
Adverse Event	14 (6%)	16 ( 6%)	16 ( 7%)	23 (10%)	30 (13%)						
Study 054	(n=218 °)	(n=216)	(n=207)	(n=213)	(n=207)						
Total Completed	79 (36%)	111 (51%)	111 (54%)	119 (56%)	118 (57%)						
Total Withdrawn	139 (64%)	105 (49%)	96 (46%)	94 (44%)	89 (43%)						
Lost to Follow-up	2 (<1%)	4 (2%)	0 (0%)	2 (<1%)	1 (<1%)						
Pre-Existing Violation	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	1 (<1%)						
Protocol Non-Compliance	5 (2%)	6 (3%)	8 ( 4%)	9 (4%)	7 (3%)						
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)						
Adverse Event	16 (7%)	17 (8%)	27 (13%)	25 (12°°)	29 (14%)						
Pooled 12-Week Pivotal Studies	(n=664 b)	(n=671)	(n=644 °)	(n=648)	(n=631)						
Total Completed	289 (44%)	397 (59%)	392 (61%)	402 (62%)	381 (60%)						
Total Withdrawn	375° (56%)	274 (41%)	252 b (39%)	246 (38%)	250 (40%)						
Last to Follow-up	10 (2%)	6 (2%)	3 (<1%)	5 (<1%)	5 (<1%)						
Pre-Existing Violation	8 (1%)	6 (2%)	1 (<1%)	4 (<1%)	2 (<1%)						
Protocol Non-Compliance	30 (4%)	18 (6%)	22 ( 3%)	15 (2%)	23 (4%)						
Treatment Failure	284 (42%)	193 (29%)	152 (24%)	153 (24%)	143 (23%)						
Adverse Event	46 ( 7%)	51 (8%)	74 (11%)	69 (11%)	77 (12%)						

Derived from Individual Study Reports

a) Includes only patients with OA of the knee.

b) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]), who were randomized into a study but did not receive study medication and are not included in the ITT Cohort.

Table A.22.2 Reasons for Study Termination (060, 087)

	Number of Osteo	arthritis Patients by T	reatment Group
		Celec	oxib
Study	Placebo	100 mg BID	200 mg QD
Study 060	(n=232)	(n=231)	(n=223)
Total Completed	146 (63%)	194 (84%)	182 (82%)
Total Withdrawn	86 (37%)	37 (16%)	41 (18%)
Lost to Follow-up	2 (<1%)	4 ( 2%)	2 (<1%)
Pre Existing Violation	2 (<1%)	2 (<1%)	2 (<1%)
Protocol Non-Compliance	6 ( 3%)	2 (<1%)	7 (3%)
Treatment Failure	56 (24%)	18 ( 8%)	21 ( 9%)
Adverse Event	20 ( 9%)	11 ( 5%)	9 ( 4%)
Study 087	(n=244)	(n=243)	(n=231)
Total Completed	164 (67%)	194 (80%)	191 (83%)
Total Withdrawn	80 (33%)	49 (20%)	40 (17%)
Lost to Follow-up	1 (<1%)	0 (0%)	1 (<1%)
Pre-Existing Violation	4 (2%)	6 (2%)	4 (2%)
Protocol Non-Compliance	8 ( 3%)	7 (3%)	5 (2%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 ( 5%)	9 (4%)	6 (3%)
Pooled 6-Week Pivotal Studies	(n=476)	(n⇒474)	(n=454)
Total Completed	310 (65%)	388 (82%)	373 (82%)
Total Withdrawn	166 (35%)	86 (18%)	81 (18%)
Lost to Follow-up	3 (1%)	4 ( 1%)	3 (1%)
Pre-Existing Violation	6 ( 1%)	8 (2%)	6 (1%)
Protocol Non-Compliance	14 ( 3%)	9 (2%)	12 ( 3%)
Treatment Failure	111 (23%)	45 (9%)	45 (10%)
Adverse Event	32 ( 7%)	20 ( 4%)	15 ( 3%)

Derived from Individual Study Reports

### Table A.23 Schedule of Observations and Procedures (Protocol 060)

	Pretreatmer	nt Period	ר	reatment Period	. <u> </u>
	Screening Visit (-14 to-2 days)	Baseline Visit (Day 0)	Week 2 (Day 14) (±2 days)	Week 6 (Day 42) (±4 days)	Early Termination
Informed Consent	x				
Medical History	x				
Physical Exam	x			X	×
Clinical Lab Tests ^a	x		x	x	x
SF-36 Health Survey		Х		X	x
OA Assessments ^b	x ^c	x	×	×	×
Discontinued NSAID or Analgesic ^d	×				
Meet Flare Criteria		×		<u> </u>	
Signs & Symptoms		x	х	x	×
Dispense Study Med		x	×		
Return & Count Study Med			x	x	×
Dispense Con Med Diary Card		х	x		
Retrieve Con Med Diary Card			. x	х	x
Blood Sample For PK ^e			×	х	

- (a) Clinical laboratory tests included: Hematology (white blood cell [WBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable]) and Biochemistry (BUN, creatinine, total bilirubin, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]). Urinalysis (pH, specific gravity, WBC, red blood cell [RBC], protein, glucose, ketones, bilirubin) at Screening Visit only. Serum pregnancy test for women of childbearing potential at Screening Visit only.
- (b) Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Pain Visual Analog Scale (VAS), Physician's Global Assessment of Arthritic Condition, Functional Capacity Classification, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Osteoarthritis Severity Index.
- (c) Screening arthritis assessment data was not collected by Searle. Patient's Assessment of Pain (VAS) and WOMAC were not performed at the Screening Visit.
- (d) Patient discontinued NSAID or analgesic use within 48 hours or at least five half-lives before the Baseline Arthritis Assessments, whichever was greater.
- (e) Blood samples were collected at selected investigational sites only.

### Table A.24.1 Patient's global assessment (protocol 087)

SC-58635 QD VS BIC EFFICACY IN KNEE 04 849 98 00 087

TABLE 19 FARTENERS GUCHAL ASSESSMENT OF ABTRECOLS PART 1 OF 4: OBSESSMEN MEANS (a) (b)

INTENT TO TREAT COMES FITT /

	PLACTEC	SC-58635 106MG BID	80-58635 2003 QB
	(tt. 243	(N [43])	(N 231)
BASELINE			•
I)	243	141	231
MEAN	3.9	3,5	3.8
STE DEV	).eo	2.53	0.60
Marketon Pre-	7.00		
WEEK 3			
n	243	241	2.81
MEAD	3.0	2.7	2,7
SID CEN	0.90	€.90	0.85
MESK o			
\$1	243	241	231
MEAN	3.0	2,₩	2.6
STD DEV	1.02	0.99	P.95

⁽a) This table is based on the lost observation carried forward approach
(b) Scale ranged from 1 (vary glod) no 1 (vary poor)

• By definition, in this and subsequent efficacy tables, the ITT concrt includes only patients who had at least one dose of study medication

	FINCEPO	SC-55635 100MG BID	90-846-33 200mb we	
	(N. 143)	(N 241)	(N 131)	g VALUE (3)
MEK 2				≈b.001
IMPROVED (b)	56(-22%)	991 41%;	714 9133	
NO CHANGE	176; 72%)	137 ( 57%)	1801 (98)	
WARRENED for	11( 58)	5 ( 2%)	9; 90°)	
Total	243:100*1	243:100%}	2313100%	
EEEK &				9.094
IMPROVED (b)	60 (-27%)	90 ( 37 <b>%</b> )	89 ( 38%)	
NO CHANGE	(604 AAR)	143 ( 59%)	143( 628)	
WIRSENED (C)	16: 790	8 ( 3%)	11 *1*)	
TOTAL	247 (1891)	141:100%;	333 (1904)	
VALUES FOR TREATHER	r comparisons (d) :			
	DIG ONCO:	298MG QC	24.0MG (QE)	
	VC.	VS.	VS.	
	FLAGEBU	FLACEBO	100MG BLD	
WEEK 1:	<0.001	5.00¥	2.107	
WEEK 6;	0.023	5,061	0.479	

⁽a) Only table is based on the last discreption bairies forward approach.

(b) Improved is defined as reduction to at least two grades from Saseline for grades 3 5 or a change in grade from 2 to 1 to Management to defined as an interest of at least two grades from Saseline for grades 3 5 or a change in grade from 2 to 1 to Management as defined as an interest of at least two grades from Saseline for grade 1 to 3 is change in grade from 4 to 5 is Combinate Management and Combinate Management () as the combinate for grades from 4 to 5 is combined from 1 to 3 is change in grade from 4 to 5 is combined from 1 to 3 is change in grade from 4 to 5 is combined from 1 to 3 is change in grade from 2 to 1 to 3 is change in grade from 2 to 1 to 3 is change in grade from 2 to 1 to 3 is change in grade from 4 to 5 is change in grade from 5 is change in

## Table A.24.2 Patient's Global Assessment (Protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE GA N49-98-02-087

TABLE 15
PATIENT'S GLOBAL ASSESSMENT OF ARTESITIS
PART 3 OF 4: MEAN CHANGE ANALYSIS (A) (5)

### INTENT: TO TREAT COHORT (ITT)

		· ·		
	PLACERO	30-53a35 190MG BID	\$0-58035 20 <b>0</b> MG QD	
	(พ. 2431	(8) - 241 }	(N-231)	p VALUE(c
Modr 1				<0.001
TESSENTED MEAN CHARGE	0.8	-1.2	$\cdot 1 \cup 1$	
STD DEV	0.99	6.99	5.94	
LS MEAN CHANGE 101	- O , P	-1.1	-1.1	
imery.				<0.001
FEEK 6 - OPSZKVRO MEAN CHANCE	-0.87	-1.1	-1.3	
STD DEV	1.10	1,06	1.05	
TE MENT CHARGE (C)	0.8	-2.1	1.2	
P-RATIO WITH 95. CONFILENC	E INTERVALS (d): 20	0MG QC VS. 100MG E1D		
MEEK BI	1	.00 ( 0.86 to 1,15)		
WEER 6:	1	.iv ( 0.96 to 3.33)		
N-VALUES FOR TREACMENT COM	(PARISONS (#):			
	100M5 FID	200MG 6E	100mg gr	
	VS.	VS.	VS.	
	PUACEBO	PLACEBO	icoma eip	
			****	
WEEK 2:	<0.001	<0.001	6,963	
WEEK 6:	୯.୭୫୫	≪0.001	0.136	

 ⁽a) This table is based on the last observation parties forward approach.
 (b) Secure ranged from 1 (very good) to 5 (very power) with pagative change indicating improvement.
 (c) Cross analysis of Covariance model with treatment and menter as factors and Baseline value as covariate, the corresponding NoVI NUB are: 0.647 for week 2, and 0.973 for week 6.
 (a) Q-PATIO is dottood as the ratio of tract science mean changes from (c), of SQ-table 200000 QD versus SQ-NW6 QD and (e) From a contrast statement from Analysis of Covariance model in (c).

## Table A.25.1 Physician's Global Assessment (protocol 087)

SC-58639 OD VS BID EFFICACY IN KNEE CA N49 98 02 087

TAGLE 17
FEYRICIANIS GLUEAL ASSESSMENT OF ARTERITIS
PART 1 OF 4: "FRENCE MEANS (a) (b)

HERET TO ISSAI COMOST (177)

	PLACEM.	.ac+56635 100 <b>m</b> g BID	211-48835 200 <b>4</b> 0-00
	(N 243)	(N. 141)	(9/231)
DASELINE			231
N	243	245	3.7
MEAN	3.8	3 . 8	
STD DEV	0,67	c.5:	, a.5%
WEER 0			
N	243	241	2 1 1
MEAN	3.0	2.6	2.7
SID DEV	0.83	⊕.8 <b>4</b>	0.73
WEEK 6			
24	243	241	231
MEAN	3.0	2.7	2.€
STD DEV	£.95	Ç.93	0.69

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 1 (very good) to 5 (very poor)

PLACERO	SC-55635 190MT BID	50-56655 13.89 ÇD	
(N 243)	(N-241)	(N. 2331	p VALUE (Š)
			40.000
47( 19%)	93 ( 39%)		
168( 77%)	144 ( 60%)		
8( 3%)	3(-1%)	1( <18)	
243(100%)	340 (100%)	231(100%)	
			0.012
691 34%)	94 ( 35%)	#9( 35 <b>%</b> )	
		151( 65%)	
12( 5%)	5 ( 2%)	0 ( 0%)	
243 (1901)	246 (100%)	231 (100%)	
COMPARISONS (d) :			
100MG BID	дромо др	200%ଠା ଜୁନ	
vs.	vs.	vs.	
PLACESO	PLACEBU	109MG E113	
	8,098	0.031	
0.022	0.004	0.913	
	(N 243)  47( 194) 188( 774)	190HT 515	180MS DID

**BEST POSSIBLE** 

⁽A) This table is based on the last ebservation cerried forward approach
(b) Improved is defined as reduction of at least two grades from Baseline for grades 2.5 or a change in grade from 2 to 100 Worsened is defined as an increase of at least two grades from Baseline for grades 1-3 or a change in grade from 4 to 5 to Cochran-Mantel-Basessal test stratified by course (Row Mean Schoes Differ)

### Table A.25.2 Physician's Global Assessment (protocol 087)

cc-Setup to no bid efficacy in size call  $80.9 \, {\rm fb} \, {\rm gr}^{2} \, {\rm gr}^{2}$ 

TABLE 13 - PYTICIANOS GLIBBO REPREMENTO DE ARTHEITIC IABT 3 (E.M.: MERR - PANAE ARRIYIZA DE CONTRA

INTERT TO THEAT COMPRESSION

	PEACERS	20-5/4,45 19 <b>093</b> BID	90.444.45 20.883.00	
	(N. 243)	(N 211)	(N 231)	g VALLE F
WIERE 2				4 49,001
SECENTED MEAN CHARGE	3.6	2.2	1.1	
+ T0+ DEV	3.90	9,47	1. AA	
ES BEAN CRASSE (C)	- (1 , 1) -	-7.1	-1.7	
WEEK A				⊀6.501
CHREEVED MEAN CHANGE	f. H	-1.1	-1.2	
STO DEV	1.61	€.3€	1.01	
LS MEAN CHANGE (C)	5.8	1.0	1.2	
( RATIO WITH 95% CONFIDENC	E INTERVALS d.: 200	MS OD VC. 100MS BID		
WEEK 3:	₹.	96 : 0.84 to 1.10%		
MEEK PF	1.	13   5.97 to 1.32)		
p-VALUES FOR TREATMENT COM	PARISONS (e):		•	
•	100MG BID	299MG (C)	200MG QD	
	Vs.	VS.	VS.	
	PLACERO	PLACEBO	TOOMS BID	
WEEL De	<0.0C1	₩8.03L	6.553	
WEEF 6:	0.003	<pre>knu031</pre>	0.105	

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with creatment and renter as factors and Baseline value as covariate,
the corresponding ROOT MSE are: 0.786 for week 1, and 0.890 for week 6
(d) Q-RATIO is defined as the ratio of least square mean changes from [c), of SC-58635 200MO QD versus SO-58635 (c)CMC RID
(e) From a contrast statement from Analysis of Covariance model in [c)

# Table A.26 Patient's Assessment of Arthritis Pain (protocol 060)

	intent-to-trea	•	
	PLACEBO	SC-58635 100mg BID	#C-58635 200m/G QD ↑
	(≈=231)	(N=231)	(N=222)
BASELINE			222
N	231	231	222
MEAN	60.1	67.8	68.0
STD DEV	15.16	16.52	16.74
WEEK 2			
N	231	231	222
MEAN	55.5	42.7	62.0
STD DEV	24.65	24.59	23.75
WEEK 6			
N	231	231	222
MEAN	54.0	40.3	41.0
ann neu	26.00	28.01	26.29

⁽a) This table is based on the last observation carried forward approach (b) Scale ranged from 0 to 100 (mm) with lower score as better

#### SC-58635 QD WS BID SFFICACY IN KNEE OA 849-96-02-060

#### TABLE 17 PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS) PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

#### INTENT-TO-TREAT COHORT (ITT)

	14.2	M1-10-170M12 4000M1 (217)		
	PLACEBO	8C-58635	SC-58635	
		100MG BID	200MG QD	
	(N=231)	(m=231)	(N=222)	p-value(c
EEK 2				<0.001
OBSERVED MEAN CHANGE	-12.6	-25.1	-25.9	
STD DEV	24.55	25,18	25.05	
LS MEAN CHANGE (c)	-12.9	-25.5	-26.1	
				<0.001
eek 6 Observed mean Change	-14.1	-27.5	-26.9	
STO DEV	25.88	27.78	28.41	
LS MEAN CHANGE (C)	-14.8	-28.5	-27.7	
2-RATIO WITH 95% CONFIDEN	CE INTERVALS (d): 200	DMC OD WE. 100MC BID		
WEEK 2:	1.	.02 ( 0.85 to 1.23)		
WEEK 61	0.	.97 ( 0.81 to 1.17)		
p-VALUES FOR TREATMENT CO	MPARISONS (e):			
	100mg BID	200MG QD	200MG QD	
	VS.	YE.	vs.	
	PLACEBO	PLACEBO	100MG BID	
WIERE 21	<0.001	<0.001	0.780	
WEEK 6:	<0.001	<0.001	0.747	

⁽a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate,
the corresponding ROOT MSE are: 23.37 for week 2, and 25.69 for week 6
(d) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 200MG QD versue SC-58635 100MG BID
(e) From a contrast statement from Analysis of Covariance model in (c)

# Table A.27 Patient's Assessment of Arthritis Pain (protocol 087)

#### INSTRUCTO TREAT CORORT (1979)

	PLACERS	SC-58635 100MG BID	23-58635 200 <b>M</b> G QD
4	(N. 243	08/141	(N 231)
BASELINE		141	291
, N	243	*** ******	65.3
MEAN	68.2	4	16.43
STD DEV	16.51	• • • •	L or 2 or 3
WEEK 2			
N	243	741	231
MEAN	54.1	43.5	44.4
STB DEV	25.33	24.19	23.96
WEEK 6			
N	243	241	231
MEAN	r5, t	45.4	42.8
STE DEV	2 % 5 %	27.61	26.55

(a) This table is based on the last chaerval to carried forward approach(b) Scale ranges from 0 to 100 perc with lower shore as Delter

#### 30-53635 QD VS BID EFFICACY IN KNZE GA N49-98-02 067

# TABLE 16 PATIENT'S ASSESSMENT OF ARTHRITIS FAIR (VAS) PART 2 OF 3: MEAN CHANGE ANALYSIS (at (b)

#### INTENT OF TREAT CONCET (ITT)

	25.Nc 2430 (N. 2431	SC-58635 100MG BID (N.241)	50~5±55 200%3 QD (N×231)	p VALUE(c)
	(14 = 2 : .			•
WHEE 2				<0.001
OBSERVED MEAN CHANGE	14.1	24.1	20.8	
STD DEV	24.75	26.35	24.44	
LS MEAN CHANGE (C)	-12.4	-22.5	-21.1	
WEEK 6				6 767
OBSERVED MEAN CHANGE	-1€.€	-22.0	-32.5	
STD DEV	27.34	28,92	28.74	
LE MEAN CHANGE (C)	15.0	-21.2	23.5	
O-RATIO WITH 95% CONFIDENC WEER 2: WEER 5:	4.	94 ( 0.76 to 1.15) 11 ( 0.86 to 1.40)		
p-VALUES FOR CREATMENT CO	ADARISONS (e).			
	100MG BIC	300mg OD	Angwa éb	
	VS.	VS.	Y5.	
	PLACEBO	PLACEBO	190MC BID	
WEEK, D:	<0.601	×0.001	0,520	
WEEK 6:	0.011	<0.001	0.344	
REET TO	V			

BEST POSSIBLE

to: This table is based on the last observation carried forward approach.

ILI Scale tanged from 0 to 100 und Aid, regalive change indicating injournment.

ICI Drow Analysis of "evariance ordel with treatent and center as factors and Baseline value as covariate, the corresponding sout Base II.41 or week 1, and 18.41 for week 6.

IN 0-BATO is Extince as the rate. I have squeek mean changes from (c), of SC-55635 200MC QD versus SC-55005 100MC RD (c) Drow a contrast statement from Analysis of Tovariance model in (c).

## Table A.28 WOMAC pain (protocol 060)

ST 58635 OD DY BOT EFFICACY IN KNEB OA N49-96-02-060

TABLE 11.1 FAMES DAIN PART 1 OF 01 CRORPORD MEANS LED 18.

INCENTAL STREAT SCHOOL (IDE)

	FLACES	50-58635 1 00: 810	80-88635 200MG QD	
	(N=701)	(N 201	(N=722)	
BASELONE			- 0 -	
31	731	23"	220	
MEAN	7.1.3	10: £	30.2	
STO DEV	3.45	3 . 49	3.6€	
WEEK 6			1.6 %	
23	231	230	224	
MEAN	5.9	7.3	7.5	
100 mg 10	8 11 C	4 (3	4	

- (a) This table is based on the last observation carried forward approach that Smalle ranged from C to DC with lower source as better.

#### THIENE-TO-THEAT COHORD (LITE)

	PLACEBO	50-58635 100MG H1D	50-58635 300 <b>M</b> S OD	
	(N=231)	(N=237)	(N=222)	p-VALUE 10
WEEK (				#8.961
CRSERVED MEAN CHANGE	- 1 . <b>4</b>	-3,0	-2, 7	
STE DEV	9.51	3.52	E . E	
LE MEAN CRANGE (C)	1.5	3.1	-2.9	
privations for treatment comparisons (d):				
	10000 810	200MG (ID	200mg gn	
	Vs.	VS.	VS.	
	FLACEBO	PLACEBO	100MS BID	
WEEK 6:	<0.001	<0.001	0.473	

- (a) This table is based on the last observation carried forward approach
  (b) Scale ranged from 0 to 30 with negative change indicating improvement
  (c) From Analysis of Covariance model with treatment and center as factors and Raseline value as devariance
  (d) From a contrast statement from Analysis of Covariance model in (c)

BEST POSSIBLE

### Table A.29 WOMAC pain (protocol 087)

SQ-88638 (D WS BID EPPICACY IN KNEE GA NAS 96 02 087

TABLE 19.1 WOMAN PAIN PART 1 OF 1: DESERVED MEANS (a) (b)

INTEND TO TREAD CORDER (1771)

	PLACEBO (N. 243)	SC-56635 130 <b>HS</b> BID	3C-58635 200M3 OD (N. 231)
		(N 241)	
PASELINE			564
27	239	239 10.1	126 10.1
MENI STD DEV	10.5 3.33	3.33	3.52
28 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			
WESK 4	2/2	240	231
51	243 8,0	7.4	7.1
MEAN SED TAN	4.11	4.47	4.08

⁽a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 20 with lower score as better

INTENT TO TELAT CHECKY (191)

	PLACERS	30 58635 100MG 315	50-5 <b>863</b> 5 20 <b>0mg od</b>	
	(≈ 243)	(5/ 141)	(N 231)	p VALUE (c)
VILK 8	. 5	2.3	3.0	<0.901
GESERVOU MEAU CHANGE SCD DEV DS MERGI CENNOE (C)	1.5 4.07 -1.6	2.6 4.32 -2.6	4.57 -3.0	
p-values for treatment comparisons (d):				
	198MG HID VE.	200MG QD Vs. Placebo	200ME OD VS. 180MG BID	
	PEACERO			
WEEK 6:	0.005	<0.002	0.276	

**BEST POSSIBLE** 

 ⁽a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 20 with negative change indicating improvement
 (c) Flom Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
 (d) Problem contrast statement from Analysis of Covariance model to 101